

# New Balance Capability Index as a Screening Tool for Mild Cognitive Impairment

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## **Abstract**

Mild cognitive impairment (MCI) is not just a prodrome to dementia, but a very important intervention point to treat Alzheimer's disease (AD). It has long been known that AD patients have a higher frequency of falls with some gait instability. Recent evidence suggests that vestibular impairment is disproportionately prevalent among individuals with MCI and dementia due to AD. Here we have developed a useful method to evaluate balance capability as well as vestibular function using Nintendo Wii balance board as a stabilometer and foam rubber on it. The new balance capability indicator, termed visual dependency index of postural stability (VPS), was highly associated with cognitive impairment assessed by MoCA, and the area under the receiver operating characteristic (ROC) curve was more than 0.8, demonstrating high sensitivity and specificity. Thus, it was proved that VPS helps screen individuals with MCI at an early and preclinical stage with high sensitivity.

## **Introduction**

Approximately 50 million people live with dementia worldwide, and this number is predicted to increase to 152 million by 2050 <sup>1</sup>. Total payments in 2020 for people age 65 and older with dementia are already beyond \$300 billion only in the US <sup>2</sup>. Thus, the burden of dementia continues to grow, and prevention strategies are highly needed.

Although our understanding of dementia etiology is still shifting, Alzheimer's disease (AD) is the most common type of dementia, accounting for an estimated 60% to 80% of cases <sup>2</sup>. The progression of AD is called the AD continuum. On this continuum, there are three broad phases: preclinical AD, mild cognitive impairment (MCI) due to AD and dementia due to AD <sup>2</sup>. A meta-analysis study found that among individuals with MCI who were tracked for 5 years or longer, 38% developed dementia <sup>3</sup>. However, in some individuals MCI reverts to normal cognition or remains stable, particularly with some appropriate intervention <sup>1</sup>. Therefore, it is important to find individuals with MCI early in the course of AD in order to protect from dementia.

Generally, individuals with dementia are vulnerable for a decline in physical functioning and basic activities of daily living <sup>4</sup>. In fact, as a characteristics of cognitive

impairment and dementia, it has long been known that AD patients have a higher frequency of falls <sup>5,6</sup>, and today, cognitive impairment is well established as an independent risk factor for falling <sup>7,8</sup>. Moreover, emerging evidence indicates that early disturbances in cognitive function are associated with slower gait and gait instability <sup>9,10</sup>. Given that gait and balance are deeply connected <sup>11</sup>, the close relationship between cognitive function and balance capability can be assumed.

The vestibular (inner ear balance) system senses head movement and orientation in space, and vestibular sensory input plays a critical role in postural control, contributing to balance capability. Intriguingly, growing evidence suggests that vestibular impairment is disproportionately prevalent among individuals with MCI and dementia due to AD <sup>12,13</sup>.

Posture in human is maintained using sensory inputs critical for balance, namely vestibular, visual, and somatosensory inputs <sup>14</sup>. Posturography is a technique used to quantify postural control in upright stance on a stabilometer. Recently, we and others have developed a useful method to evaluate balance capability as well as vestibular function using a stabilometer and foam rubber <sup>15-17</sup>. With further modifications to this method, here we report a new balance capability indicator, named visual dependency index of postural stability (VPS), which is highly associated with

cognitive impairment and helps screen individuals with MCI.

## **Results**

### **Wii balance board (WBB) has the same performance as an authentic stabilometer**

Because the final goal of our project is to implement an inexpensive MCI screening system to prevent dementia, we started from developing a new posturographic system utilizing Wii balance board (WBB), a Nintendo game machine available at a very low cost (lower than \$100). According to several previous reports where WBB was tested in a clinical setting to track and record the center of pressure (COP) of subjects<sup>18-20</sup>, we developed a new software run on windows PC to measure and calculate index of postural stability (IPS) values (Figure 1A)<sup>15,17</sup>. As expected, WBB showed an excellent performance to measure IPS values as accurately as an authentic stabilometer for medical use (GP-6000 gravicorder), as shown in Figure 1B.

### **VPS and cognitive function show a significant relationship**

Next, we devised a new indicator of postural stability that is more associated with vestibular function, based on the previous reports: combination of IPS<sup>15</sup> and utilization of foam rubber as well as eye closure<sup>16,17,21</sup>. The resultant new indicator, named visual dependency index of postural stability (VPS), was defined as the ratio of

eye-opened vs. eye-closed IPS values measured on foam rubber.

Using VPS, the new indicator of vestibular function calculated from balance measurement, we examined the possible association between vestibular function and cognitive impairment. Table 1 showed the clinical characteristics of the study participants, basically healthy volunteers (n=49). Japanese version of the Montreal Cognitive Assessment (MoCA) was used to assess cognitive function<sup>22,23</sup>. It is widely accepted that MoCA is superior to MMSE in the detection of MCI as the MMSE has lower sensitivity<sup>23,24</sup>. In fact, as shown in Table 2, both the normal and MCI groups diagnosed based on MoCA showed nearly full score (30 points) on MMSE. As shown in Figure 2A, VPS values exhibited a significant negative correlation with MoCA scores. Also, significant association was observed between VPS and TMT-B scores, another scoring method to evaluate cognitive function (Figure 2B,C).

### **MCI group has significantly higher VPS**

In accordance with the above result, when participants were categorized into two groups of normal (MoCA  $\geq$  26) and MCI (MoCA  $\leq$  25), MCI group showed significantly higher VPS values (Figure 3A), despite no differences in IPS values between the groups (Figure 3B). All the other items were not significantly different

between the two groups (Table 1).

### **ROC curve shows good sensitivity and specificity**

The result of the receiver operating characteristic (ROC) analysis was shown in Figure 4. As shown there, area under of the curve (AUC) was more than 0.8, indicating a good sensitivity and specificity in general. The VPS cutoff value obtained from the maximum value of the Youden Index was 1.00 (sensitivity; 81.3%, specificity: 57.6%, 95% confidential interval: 0.675 – 0.936). In other words, if it exceeds the cutoff value of 1.00, it is highly likely that it is MCI, and conversely, if it is below it, it is highly likely that it is not MCI.

## Discussion

In the present study, we clearly demonstrated that our new balance indicator VPS is useful to screen individuals with MCI with high sensitivity.

The new indicator VPS (visual dependency index of postural stability) was created from the combination of IPS (index of postural stability) quantification method<sup>15,17</sup> and foam posturography technique<sup>16</sup>, both established previously. Among three sensory inputs critical for balance, namely vestibular, visual, and somatosensory inputs<sup>14</sup>, the usage of foam rubber disrupts the somatosensory input, and eye closure additionally eliminates visual input. Therefore, it is assumed that vestibular function can easily be assessed on foam rubber with eye-closed condition<sup>16</sup>. Although we have not checked the point by ourselves, they examined the relationship between foam posturography data and direct vestibular function tests using cervical vestibular evoked myogenic potentials (cVEMPs), a well-established clinical test to examine vestibular function, and concluded that foam posturography on an eye-closed condition was useful for assessing vestibular impairment with abnormal cVEMPs<sup>21</sup>. Further taking the ratio between eye-closed and -opened conditions, we managed to raise the accuracy of measurement and named the value VPS.

Regarding the relationship between vestibular dysfunction and cognitive impairment, emerging evidence suggests that vestibular loss is disproportionately prevalent among individuals with MCI and dementia due to AD <sup>12,13,25</sup>; in a study named Baltimore Longitudinal Study of Aging (BLSA), testing 183 healthy community-dwelling participants with a mean age of 72, they found that poorer vestibular function was significantly associated with poorer cognitive function assessed by several testing including TMT-B <sup>12</sup>. In addition, it has previously been shown that vestibular loss causes hippocampal atrophy and impaired spatial memory in humans <sup>26</sup>. A further study in BLSA found that poorer vestibular function was associated with significantly reduced hippocampal volume <sup>27</sup>. Thus, hippocampal atrophy may underlie the link between vestibular loss and cognitive decline.

Related to the link between vestibular and cognitive functions, hearing impairment is also reported to be linked with cognitive decline; a small US prospective cohort study of 194 adults without baseline cognitive impairment and at least two brain MRIs with a mean of 19 years follow-up, found that midlife hearing impairment measured by audiometry is associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal cortex <sup>28</sup>. The positive association between the loss of inner ear function and cognitive impairment is noteworthy.

Considering further in this regard, inner ear dysfunction and hippocampal atrophy might have some underlying pathological processes shared in common. The hippocampus has been known as one of the limited areas in the adult mammalian brain where neurogenesis normally occurs<sup>29</sup>, and it is widely acknowledged that hippocampal neurogenesis is impaired in AD, which plays a role in cognitive decline<sup>30,31</sup>. On the other hand, recent evidence suggests that reactive adult neurogenesis occurs in sensory systems following damages to the sensory nerve, and in fact this mechanism promotes balance recovery after vestibular loss<sup>32</sup>. Thus, it is conceivable that some common disorder related to neurogenesis in AD might underlie the link between inner ear dysfunction and hippocampal atrophy. Although currently this is just a hypothesis and further investigation is needed to prove it, this hypothesis might be related to the fact that AD is also strongly associated with olfactory dysfunction<sup>33-36</sup>, given that olfactory bulb is another area of the adult brain where neurogenesis occurs vigorously<sup>29</sup> and patients with AD exhibit smaller olfactory bulb volumes<sup>37</sup>.

MCI is not just a prodrome to dementia, but a very important intervention point to treat AD. Recently, aducanumab, an antibody drug targeting A $\beta$ <sup>38</sup>, was approved by FDA in the US<sup>39</sup>. This decision made aducanumab the first new drug to be approved for the treatment of AD since 2003 and the first drug to ever be approved for modification

of the course of AD. Since the drug is targeting MCI and early AD, the demand for efficient screening of MCI patients will become larger in the near future.

Because we started this project to realize an inexpensive and easy-to-use MCI screening system, we focused on WBB, a very popular Nintendo game machine, and successfully proved that it can be used as an excellent stabilometer that has the same performance as an authentic apparatus approved for the medical use. Nintendo has so far sold out more than 37 million WBB worldwide (<https://www.nintendo.co.jp/ir/pdf/2009/091030.pdf>). It means a huge potential for the novel approach to diagnose MCI at an earlier stage.

In summary, we developed a new balance capability index termed VPS using WBB as a stabilometer. This method is useful to screen individuals with MCI at an early and preclinical stage with high sensitivity.

## **Methods**

**Participants** — From December 2020 to February 2021, we enrolled 49 participants with healthy conditions who were 56 to 75 years old and had no clinically apparent cognitive impairment. The participants were recruited using our department’s website, bulletin boards at our university, and a local community magazine. Participants were paid a reward of 7,000 yen. Exclusion criteria included (i) history of chronic diseases (dementia, diabetes, kidney disease, collagen disease, peripheral neuropathy); (ii) Having a disability certificate or using long-term care insurance; (iii) being unable to walk independently without assistive devices (including transportation). No one was excluded based on results of cognitive function tests. Written informed consent was obtained from participants prior to study enrollment. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of University of Tsukuba Hospital (R02-251).

**Clinical Evaluation** — Participants were surveyed for age, sex, exercise habitation, alcohol drinking habitation, working, driving. Body composition was evaluated by bioelectrical impedance analysis (InBody 720, BioSpace, Tokyo). Body mass index

(BMI) and skeletal muscle mass index were calculated by dividing the body weight (kg) by the square of the height (m<sup>2</sup>) and dividing the limb skeletal muscle mass (kg) by the square of the height (m<sup>2</sup>), respectively.

**Assessment of Cognitive Function** — Global cognitive function was assessed using the Japanese version of the Montreal Cognitive Assessment (MoCA) <sup>22,23</sup> and the Mini-Mental State Examination (MMSE) <sup>40</sup>. Based on MoCA, participants were categorized into two groups of normal (MoCA  $\geq$  26) and MCI (MoCA  $\leq$  25). Trail Making Test parts A and B (TMT-A/-B) were used for assessing processing speed and executive function, respectively <sup>41</sup>. Clinical dementia rating (CDR) were used as an observational scale to assess the severity of dementia <sup>42-44</sup>.

**Assessment of Balance capabilities** — Balance capabilities were assessed by the index of postural stability (IPS) and the visual dependency index of postural stability (VPS). IPS and VPS were measured using a stabilometer as described previously <sup>17</sup>. As a stabilometer, GP-6000 gravicorder (Anima Co., Tokyo, Japan) and Wii balance board (WBB; Nintendo Co, Kyoto, Japan) were used. Briefly, IPS was measured as follows; first, the participants stood in a resting position with the inside of the foot at a distance

of 10 cm on the stabilometer to measure the instantaneous fluctuations in the center of pressure (COP). Then, participants were instructed to incline the body to the front, rear, right and left keeping the body straight and without moving the feet for 10 seconds at each position, and the instantaneous fluctuations in COP were recorded. IPS was calculated as  $\log [(area\ of\ stability\ limit + area\ of\ postural\ sway) / area\ of\ postural\ sway]$ . Area of stability limit was calculated as the front and rear center movement distance between anterior and posterior positions  $\times$  the distance between right and left positions. Area of postural sway was calculated as average measurement value in 10 seconds under anterior, posterior, right, left and center positions. The area of postural sway was calculated as the mean sway area of the 5 positions. Visual dependency index of postural stability (VPS) was defined as the ratio of eye-opened vs. eye-closed IPS values measured on foam rubber. VPS values are age-adjusted by the following formula: age-adjusted VPS =  $V / V'$ , where

$V$  (measured VPS) = eye-opened IPS / eye-closed IPS,  $V'$  (age-predicted VPS) =  $O / C$ ,

$O$  (age-predicted eye-opened IPS) =  $-0.0003 \times age^2 + 0.0145 \times age + 1.1602$

(Supplementary Figure S1) and

$C$  (age-predicted eye-closed IPS) =  $-0.00006 \times age^2 - 0.0037 \times age + 0.8805$

(Supplementary Figure S2).

For a measurement using WBB, WBB was connected wirelessly with a Bluetooth adapter to a laptop computer. Raw data were collected simultaneously, stored and processed using custom-written software (Penguin system Co, Ibaraki, Japan).

**Statistical analyses** — Based on distribution, continuous variables were expressed as deviation or median (interquartile range) and compared using the unpaired *t*-test or the Mann-Whitney *U*-test for two-group comparisons. Categorical variables are expressed as numerals and percentages and were compared with Fisher's exact test. Spearman's rank correlation coefficient was used to examine bivariate associations between tests of cognitive function and balance capability. Pearson's correlation coefficient was used to examine bivariate associations between IPS of the GP-6000 gravicorder and that of WBB. Regarding the receiver operating characteristic (ROC) analysis, the VPS value and 01 classification (0 for Normal group, 1 for MCI group) for the presence or absence of MCI, the cutoff value, sensitivity, specificity, and area under of the curve (AUC) for the presence or absence of MCI were calculated. The cutoff value was decided by the point where the Youdem Index reaches the maximum value. Statistical analyses were performed using SPSS Statistics 26 (Chicago, IL, USA). Statistical significance was considered at a value of  $<0.05$ .

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## **Author contributions**

Y.S. and N.Y. conceived the study. Y.S. T.T. and K.N. performed the study and analyzed the data together with N.Y. Y.S. and N.Y. co-wrote the paper. All authors discussed the results and commented on the manuscript.

## **Competing interests**

The authors declare no competing financial and non-financial interests.

## Figure legends

### **Figure 1. WBB has the same performance as an authentic stabilometer.**

(A) Schematic representation of the IPS measurement system using WBB.

(B) Correlation between IPS values measured by an authentic stabilometer (GP-6000 gravicorder) and those by WBB is shown (n=49). IPS, index of postural stability; VPS, visual dependency index of postural stability; WBB, Wii balance board.

### **Figure 2. VPS and cognitive function show a significant relationship.**

Correlation between test VPS and cognitive function is shown. Cognitive function is assessed by (A) MoCA, (B) TMT-A and (C) TMT-B. VPS, visual dependency index of postural stability; MoCA, Montreal cognitive assessment; TMT-A, trail making test part A; TMT-B, trail making test part B.

### **Figure 3. MCI group has significantly higher VPS.**

Comparison of the normal group and the MCI group is shown. Data are analyzed by the Un paired T-test.  $*P < 0.01$ . MCI, mild cognitive impairment; IPS, index of postural stability; VPS, visual dependency index of postural stability.

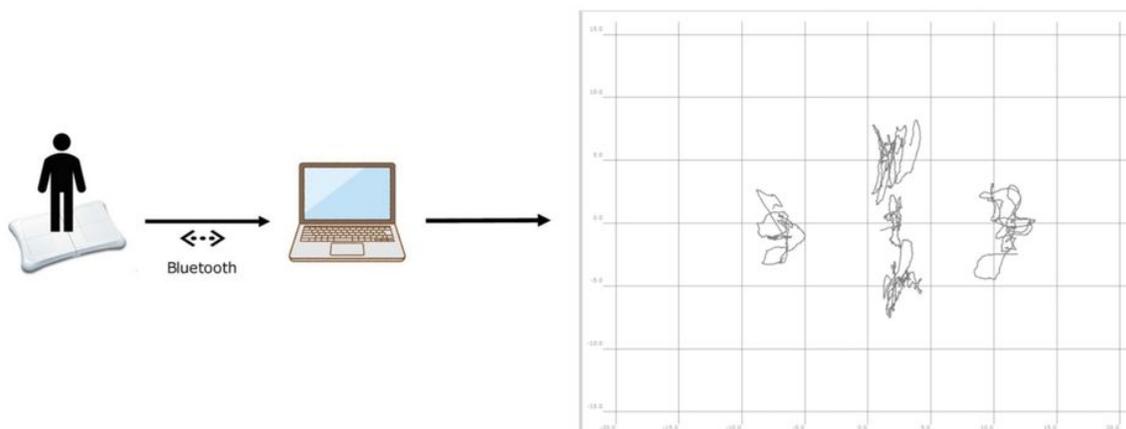
**Figure 4. ROC curve shows good sensitivity and specificity.**

ROC curve of VPS is drawn to discriminate MCI from normal. ROC, receiver operating characteristic; VPS, visual dependency index of postural stability; MCI, mild cognitive impairment; AUC, area under the curve.

# Figures

Figure 1

A



B

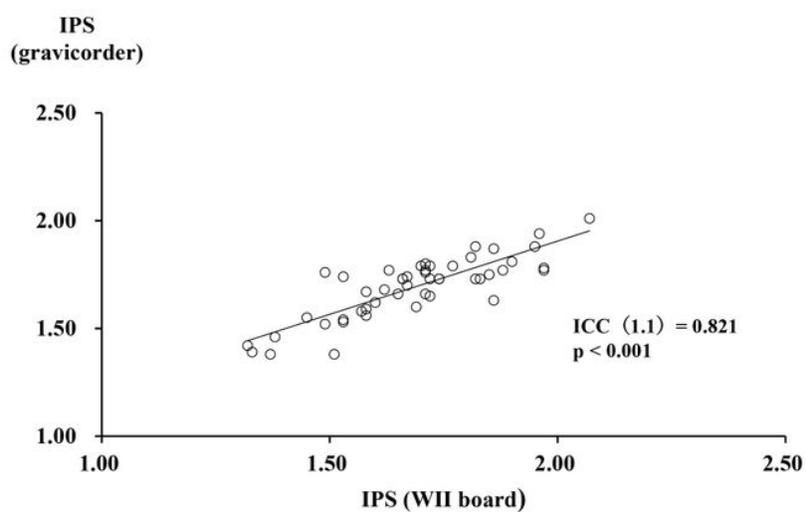


Figure 1

WBB has the same performance as an authentic stabilometer. (A) Schematic representation of the IPS measurement system using WBB. (B) Correlation between IPS values measured by an authentic stabilometer (GP-6000 gravicorder) and those by WBB is shown (n=49). IPS, index of postural stability; VPS, visual dependency index of postural stability; WBB, Wii balance board.

Figure 2

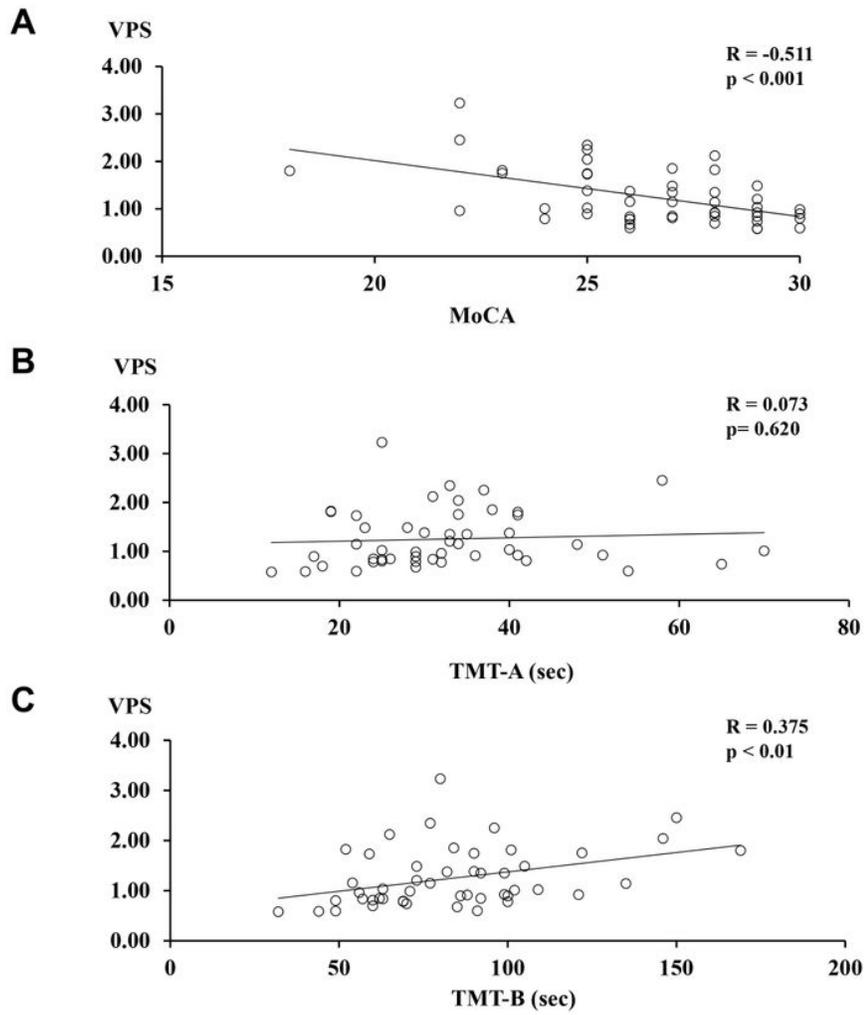
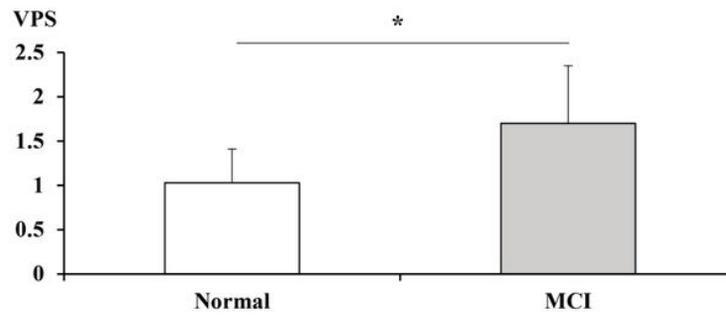


Figure 2

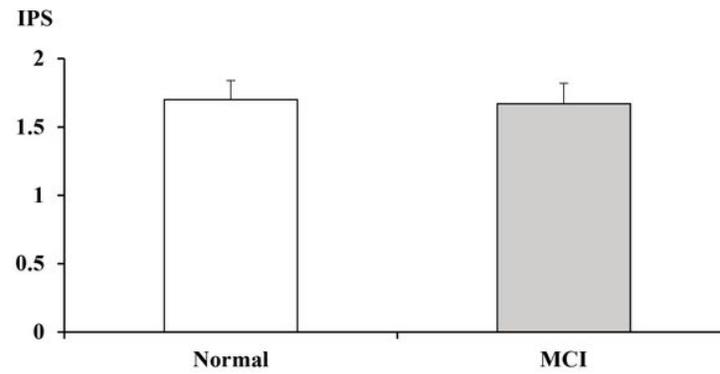
VPS and cognitive function show a significant relationship. Correlation between test VPS and cognitive function is shown. Cognitive function is assessed by (A) MoCA, (B) TMT-A and (C) TMT-B. VPS, visual dependency index of postural stability; MoCA, Montreal cognitive assessment; TMT-A, trail making test part A; TMT-B, trail making test part B.

**Figure 3**

**A**



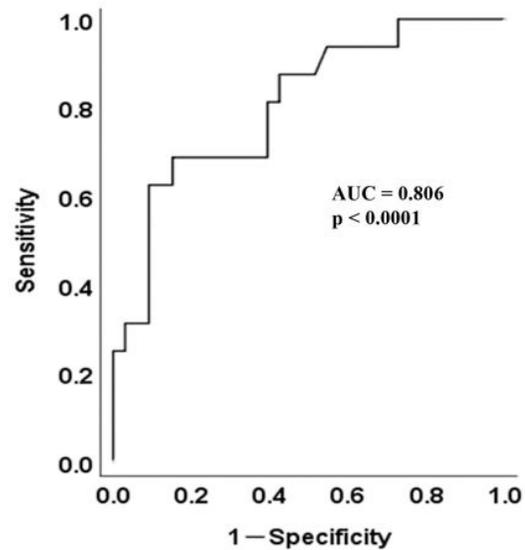
**B**



**Figure 3**

MCI group has significantly higher VPS. Comparison of the normal group and the MCI group is shown. Data are analyzed by the Un paired T-test. \*P < 0.01. MCI, mild cognitive impairment; IPS, index of postural stability; VPS, visual dependency index of postural stability

**Figure 4**



**Figure 4**

ROC curve shows good sensitivity and specificity. ROC curve of VPS is drawn to discriminate MCI from normal. ROC, receiver operating characteristic; VPS, visual dependency index of postural stability; MCI, mild cognitive impairment; AUC, area under the curve

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryInformation.pdf](#)